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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/873,601	06/12/97	NOLAN G	

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EXAMINER	
RICIGLIANO	

ART UNIT	PAPER NUMBER
1713	

DATE MAILED: 08/06/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/873,601	NOLAN et al.
Examiner	**Group Art Unit**
Joseph W. Ricigliano Ph. D.	1618

☒ Responsive to communication(s) filed on *5/10/99 and 12/31/99*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-42* is/are pending in the application.

Of the above, claim(s) *9-26, 29, 30, 33, 35-38, and 40-42* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-8, 27, 28, 31, 32, 34, and 39* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

KEITH D. MacMILLAN
PRIMARY EXAMINER

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

This action is responsive to the communications received 5/10/99 and 12/31/99.

1. With respect to the response to the Notice to comply with the sequence rules, it is noted that the CRF has been received and is technically correct.

Election/Restriction

2. Applicants' election of a species for prosecution on the merits consisting of Ai, Bii and Cii in paper number 15 is aknowledged.

3. Applicants indicate that claims 1-8 and 27-42 are pending in the application in paper number 15, response of 5/5/99. However, there is no indication that any claims have been canceled and claims 1-42 appear to be pending. Clarification concerning the status of pending claims is requested in order to clarify the record.

4. Generic claims 1-8 and 27 and species specific claims 28, 31-32, 34 and 39 are being examined on their merits.

5. Claim 9-26, 29-30, 33, 35-38, and 40-42 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected inventions or species. Election was made **without** traverse in Papers No. 7 and number 15.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-8, 27 28, 31-32, 34 and 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-8, 27 28, 31-32, 34 and 39 have been amended to recite that the scaffolds are exogenous scaffolds having no enzymatic activity. There is no indication where support for this amendment may be found in the disclosure as originally filed. Applicants can overcome this rejection by indicating by line and page number where support can be found in the disclosure as originally filed for the amendment.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 8, 31, 32, 43 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 8 is indefinite in reciting "an exogenous bioactive agent precursor" as it is unclear of what the limitations of an "exogenous bioactive agent precursor" are. The definitions set forth on pages 34-36 of the specification fail to aid in clearly defining the limits of this term. Based upon the definition it appears that any molecule would be bioactive agent precursor if could be incorporated into a bioactive agent. Under applicants definition even water which is added during reactions such as an esterase or amidase (protease) reaction or through hydrogen exchange would constitute a bioactive agent precursor. Furthermore, sugars, amino acids, or reduced flavin

or pyridine nucleotides which donate reducing equivalents and a hydrogen atom (e.g, in the reduction of a carbonyl to an alcohol etc.) would appear to be bioactive agent precursors. Therefore, the term bioactive agents is indefinite, not because it is broad, but because it is not possible to determine what is or is not "a bioactive agent precursor" and hence it is not possible to determine the metes and bounds of the invention as claimed.

11. Claims 31, 32, 34, and 39 recite a fusion partner is present in the composition. This term is vague and indefinite as it is unclear what the metes and bounds of a fusion partner are. Applicants' definition on page 16 of the specification sets forth: "[B]y 'fusion partner' herein is meant a sequence that is associated with either the nucleic acid or the expression product that confers a common function or ability. This is indefinite for numerous reasons. First, does the adjective "common" modify only "function" or the phrase "function or ability." Second, what is common about the "function" or the "function or ability." Third, the fusion partner is stated as a "sequence that is associated with either the nucleic acid or the expression product." Which nucleic acid is "the nucleic acid" as the claims as dependent from claim 1 do not require a nucleic acid at all? Moreover, the "expression product" is vague and indefinite as it is unclear what is being expressed. This statement appears to presuppose that the scaffold must be able to express an RNA (Or do applicants intend this to presuppose expression of a protein?). Furthermore, it is unclear what the limitations of "asssociated" are in this definition. For example, consider the case of a nucleic acid scaffold which encodes an enzyme having a nuclear localization sequence wherein the enzyme binds to the nucleic acid itself (e.g., the adenovirus polymerase). Is the sequence encoded by the nucleic acid a fusion partner of the nucleic acid or the protein? Clearly

the nucleic acid (adenovirus genome) is associated with the "fusion partner" (nuclear localization sequence) by coding for it, and in addition the expressed polymerase is associated with it as it is part of the polymerase protein. However, as the polymerase also binds to the nucleic acid it can be viewed as being associated with the nuclear localization sequence through the protein. As it is not possible to determine what defines a fusion partner, it is not possible to determine the metes and bounds of the invention as claimed.

Claims 1-8, 27-28, 31-32, 34 and 39 recite the use of "exogenous scaffolds" as used this term is vague and indefinite because exogenous has more than one meaning. Exogenous as defined by Webster's Collegiate Dictionary can mean Produced by growth from superficial tissue or introduced from or produced outside the organism or system. Therefore, the term "exogenous scaffold" as used could refer to any support material as long as it has binding sites for the said enzymes. This could include beads, filter disks, enzymer reactor surfaces or materials used for immunoprecipitationas long as they have specific binding sites comprised of partners for the enzymes (such as antibodies, biotin or protein A for example). Alternatively, the term could be taken to mean an a protein introduced extracellularly. In addition, applicants utilize the term exogenous to mean heterologous (page 14, line 23). As it is not possible to determine what limitations are intended by the term "exogenous scaffold" it is not possible to determine the metes and bounds of the invention as claimed.

Claim Rejections - 35 USC § 101

12. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

13. Claims 1-8, 27-28 31-32 34 and 39 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Applicants claims recite a cell containing composition comprising an exogenous scaffold, first and second binding sites and at least a first and second enzyme with affinity for a binding the site.

A cell containing composition reads on a animal and wild type adenovirus infects animal cells in nature. Moreover it is known that adenovirus infected cells have the adenovirus genome which is a scaffold with no enzymatic activity. The genome has binding sites for the adenovirus DNA polymerase which is expressed by the virus and is heterologous to the cell. The genome also has numerous binding sites for RNA polymerase (a second enzyme) such as the E1A, E1B, E2a, E2B, E3 and E4 promoters (see figure 11). In addition the viral genome is a nucleic acid which encodes the scaffold nucleic acid. The binding sites are present on each molecule of the genome and numerous copies of the genome are present in an infected cell. The virus infected cells contain partially assembled virions in addition to partly assembled viral protein, unprocessed or partially processed viral pre-mRNA molecules and partially replicated viral DNA strands, hence the cells contain exogenous bioactive precursors. Adenovirus infects mammalian cells and has a linear genome. Applicants have defined fusion partners as a sequence that is associated with the nucleic acid or the expression product that confers common function or ability on page 16 of the specification. Hence, the promoters, promoter elements or the terminal proteins of

adenovirus can be considered fusion partners of the scaffold. Moreover, the sequences of the proteins related to their enzymatic activity and nuclear localization are fusion partners under applicants definition hence claim 32 is anticipated. In that the adenovirus polymerase contains nuclear localization sequences. See the teachings of Horowitz (1991) and Padmanabhan (1991). Hence, the claims read on adenovirus infected cell, which are known natural products, and thus they are not statutory subject matter.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-8, 27-28, 31-32, 34 and 39 are rejected under 35 U.S.C. 102(e) as being anticipated by Khosla et al. (US 5,672,491) for reasons of record in the rejection of claims 1-8 as being anticipated by Khosla et al under 35 USC 102(e) in paper number 8.

Khosla et al. teach recombinant production of novel polyketides. This reference teaches that two general classes of polyketide synthase ("PKS") exist, with the type I PKSs including assemblies of several large multifunctional proteins, and is represented by the PKSs for macrolides such as erythromycin (see column 1, lines 59-64). This reference teaches that host cells lacking their native PKS gene cluster may be transformed with a replacement PKS gene cluster, which

may be hybrid and include both type I and/or type II PKSs, and one may include as many genes as desired (see column 8). This reference teaches that 6-deoxyerythronolide B synthase (DEBS) catalyzed the biosynthesis of an erythromycin aglycone, and the polypeptides for DEBS are encoded in three open reading frames which are organized into modules, which also include an acyltransferase, β-ketoacyl carrier protein synthase, and others (see column 15, and Figure 9). Finally, this reference specifically exemplifies transformation of a *Streptomyces coelicolor* host cell with DEBS PKS genes (see column 27, Example 5). Thus, as this reference teaches that the type I PKSs including assemblies of several large multifunctional proteins, and is represented by the PKSs for macrolides such as erythromycin, and specifically teaches a cell transformed with the DEBS PKS genes, which contains at a minimum 3 polypeptides, this reads on one of the polypeptides encoded by the open reading frames being the exogenous scaffold comprising at least a first binding site and a second binding site, with the other two polypeptides encoded by the other two open reading frames being the first and second enzymes, both heterologous to the cell, being bound to the binding sites of the first polypeptide. In addition, although this reference does not explicitly state, the other enzymes of the module, i.e. the an acyltransferase, β-ketoacyl carrier protein synthase, and others, are most likely associated with the complex, and would read on a scaffold having 3-5 binding sites, wherein the scaffold may be the same of different molecules. This would be an inherent property of the PKS complex encoded by the module.

15. Applicant's arguments filed 12/31/98 have been fully considered but they are not persuasive.

Applicants assert that they have amended the claim to recite that the scaffolds have no enzymatic activity hence the rejection of record should be withdrawn as it does not meet all of the limitations of the invention as claimed. However, in view of rejection of the instant claims under 112 first paragraph of introducing new matter n reference to the said amendment the rejection of record is maintained. Applicants can overcome this rejection by indicating where support for amendment which recites that the scaffolds have no enzymatic activity can be found in the disclosure as originally filed.

16. Claims 1-8, 27-28, 31-32, 34 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Horowitz (In "Fundemantal Virology 2nd edition" Eds. Fields et al. 1991) as evidenced by the teachings of Padmanabahn et al. (New Biol. 1991).

Applicants' invention is directed to a cell containing a composition comprising an exogenous scaffold, first and second binding sites and at least a first and second enzyme with affinity for a binding the site.

Horowitz teaches that adenovirus infects intact animal and can be used to infected mammalian cells such as HeLa cells (page 776 column 1 lines 34-36). Infected cells have the adenovirus genome which is a scaffold with no enzymatic activity. The genome has binding sites for the adenovirus DNA polymerase which is expressed by the virus and is heterologous to the cell. The genome also has numerous binding sites for RNA polymerase (a second enzyme) such as the E1A, E1B, E2a, E2B, E3 and E4 promoters (see figure 11). Therefore, Horowitz anticipates claims 1 and 3-5. As the virus genome is a nucleic acid which encodes the scaffold nucleic acid which encodes the scaffold claim 2 is also anticipated. As the binding sites are

present on each molecule of the genome claim 6 is anticipated and as numerous copies of the genome are present in an infected cell the binding sites are also present on different scaffolds as required by claim 7. The virus infected cells contain partially assembled virions in addition to partly assembled viral protein, unprocessed or partially processed viral pre-mRNA molecules and partially replicated viral DNA strands, hence the cells contain exogenous bioactive precursors as required by claim 8. As adenovirus infects mammals cells and has a linear genome claims 27 and 28 are anticipated. Applicants have defined fusion partners as "a sequence that is associated either with the nucleic acid or the expression product that confers a common function or ability" at page 16 of the specification. Hence, the promoters, promoter elements or the terminal proteins of adenovirus can be considered fusion partners of the scaffold as required by claims 31. Moreover, the sequences of the proteins related to their enzymatic activity are fusion partners under applicants definition hence claim 32 is anticipated. In that the adenovirus polymerase contains nuclear localization sequences. Therefore, claims 1-8, 27-28, 31 and 32 are clearly anticipated by the teachings of Horowitz.

In addition, the scaffolds the nucleic acid of the adenovirus genome code for the adenovirus polymerase which has nuclear localization sequences in the polymerase gene which are expressed in the expression product. Hence, both the scaffold and the adenovirus polymerase both comprise a comprise a fusion partner (as evidenced by Padmanabahn et al). Thus the adenovirus infected cells described by Horowitz would inherently meet the limitations of claims 32, 34 and 39.

17. In view of the fact that Bott et al does not disclose cell containing composition the rejection of claims 1-8 under 35 U.S.C. 103(a) as being unpatentable over Bott et al. (WO 97/14789).

18. Ricard et al. teach that there is now experimental evidence that association of different enzymes as a multienzyme complex may result in alteration of the catalytic activities of the enzymes within the complex.

19. Khosla et al., WO 95/08548, is the published PCT, whose disclosure is basically the same as Khosla et al. (US 5,672,491).

20. It is noted that no 1449 appeard to accompany the supplemental IDS filed 3/29/99. Applicants are requested to provide a 1449 so that the record may clearly reflect the consideration of the references.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph W. Ricigliano Ph. D. whose telephone number is (703) 308-9346. The examiner can be reached on Monday through Thursday from 7:00 A.M. to 5:30 P.M.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703) 308-0196.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Donald E. Adams Ph. D., can be reached at (703) 308-0570.

Joseph W. Ricigliano Ph. D.

KEITH D. MacMILLAN
PRIMARY EXAMINER